

09/320637
#7

Attorney's Docket No. 3339-239A

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Joel Sternheimer

Appl. No.: 09/320,637

Group Art Unit: 1633

Filed: May 26, 1999

Examiner: J. Martinell

For: METHOD FOR THE REGULATION OF
PROTEIN BIOSYNTHESIS

Commissioner for Patents
Washington, DC 20231

DECLARATION UNDER 37 C.F.R. 1.132

Sir:

I, JOËL STERNHEIMER, do hereby declare and say as follows:

1. That I am a graduate of Paris, Lyons and Princeton Universities and received my degrees in the years 1964, 1966 and 1967 (Doctorate in 1966). My Curriculum Vitae and the list of publications are attached thereto to my declaration dated May 19, 1999 attached hereto as Annex 1.

2. That I am the inventor of the subject matter of United States patent application Ser.No. 09/320,637.

3. That I have read the Office Action of May 25, 2001; that this Declaration is intended to set forth the fact that my invention has utility and that the claims are not vague, indefinite, incomplete or incomprehensible.

4. The sounds defined in the instant invention are different from music. The sounds or proteodies of the instant invention can not be memorisable, this being contrary to music. Man composed melodies follow cognitive constraints of a statistical nature, which clearly separate them from sequences of frequency intervals as they may be computed from protein elongation processes. (Annex 2). For their part, the proteodies provide in the sequence of frequency intervals from one sound to the following one a scale-invariant information identical to the one which is present in protein synthesis process, and act on it by scale-resonance. Therefore, sounds or proteodies of the instant invention are effectively not music.



Considered
12/19/01
[Signature]

5. I understand that the claims have been rejected because the disclosed invention is inoperative and therefore lacks utility. This is simply not so. The claims do not lack utility. The method of the invention allows and controls the *in situ* regulation of the synthesis of selected protein.

6. The specification shows utility in the following manner. Many disorders in living beings may be related to an imbalance in protein synthesis. Therefore, restoring this balance will at least contribute or even suffice to cure these disorders, by stimulating or inhibiting the right proteins. As for human diseases, this is especially useful in that thanks to its audibility, the treatment may be controlled by the patient himself. These explanations are well supported in the specification, for instance pages 25, lines 6 sqq, lines 12 sqq, page 26, lines 26 sqq, page 28, lines 28 sqq.

7. As explained in my first declaration (Sternheimer I, Annex 1), by way of example, it was undertaken by Mr. Pedro Ferrandiz under my supervision to stimulate the growth of blue-green algae –prokaryotes, genus *Anabaena*- by epigenetic regulation. See Annex 3. Their photosynthetic activity involves in particular pigmentary proteins (cyanins). Thus their biosynthesis is easily observed through color change and oxygen release. Since these bubbles had the property to revive the flame of a lighted match which was put close by, we concluded they contained oxygen. On May 24th there were about 70 surface bubbles and on the 28th they were 130 (Figure 4). We point out that the maximum number of visible bubbles observed in the control vat is 8. Hence there is more than a factor 16 between the two cultures with respect to oxygen release. In fact the medium of the musical culture was saturated with oxygen at the end of the observation time. Clearly this is correlated to an increase of the photosynthetic activity in the musical vat. It indicates that while the oxygen was released some carbonated composites have been fixed (Figure 5, taken six months later). Thus this particular application of the epigenetic regulation process led to an interesting depollutive system. This should beget further interests.

8. Also, my Declaration, Sternheimer I shows in Annex 9 thereof, Figure which is a comparative test: On the left side (control): non treated tomatoes. On the right side: tomatoes having received during 16 days 3 minutes per day, the music of protein of anti drought protein

TAS14. Both control tomatoes and the treated tomatoes having 1 ½ litres of water per plant per day. The experiment was replicated in a greenhouse in Grand University by M. Yannick van Doorne, for his thesis in agriculture and bioengineering. He carefully measured all possibly relevant parameters, such as temperature and moisture for both treated and untreated tomatoes and was able to preclude with over 99% probability any of these alternative parameters as the cause of the difference observed; therefore, he was able to conclude that the observed effect was indeed due to the sound treatment. These conditions constitute, therefore, clearly a controlled study.

9. The examiner contends there is no phase in polypeptide elongation, but since various growing nascent polypeptide chains may be seen at a given time in various states of elongation, they are "presumably" also in different phases of elongation. A lot of available evidence contradicts this assumption. First, a periodicity is clearly visible on polyribosomes), and where there is a period, there is a phase. (See Annex 3, figure 1 from B. Alberts et al., Molecular Biology of the Cell, Garland Publishing, New York and London, 3rd edition 1994, p. 238. See annex 4. Second, the existence of a phase in protein synthesis may be checked by comparison with the pauses in elongation as determined from accumulation of intermediate nascent chains of discrete sizes, which may be observed using gel electrophoresis. (See, such as in the work of S. Varenne et al. (J. Mol. Biol. 180, 549-576, 1984), Annex _____. In the example given in this paper on pFW 565 (E. Coli's outer membrane protein A), pauses may not only be seen to fit the musical "cadences" located as explained in patent application (note the average period of amino acids near the maximum amplitude, *i.e.*, maximum number of intermediate nascent chains). The mere fact that they follow a regular pattern, as seen on figure 2 in contradistinction with the predictions of codon usage (which postulate that codon-anticodon binding follows a trial-and-error procedure, wherefrom pauses would simply be statistically correlated with rare codons, yielding a chaotic-like behavior), is by itself evidence of a phase, already in the case of bacteria, with "some" undetermined mechanism to control it – for which inventor's theoretically grounded scaling waves do provide an explanation (the theoretical papers are quoted in application, p. 1 and p.2).

10. In evolved organisms, amino acids are carried through the blood, and are thus subject

heartbeat's phase. Here there is direct evidence that this very phase also governs polypeptide elongation. Actually, heartbeat phase is easily detected using radial pulse, and it has been observed by Dr. N'guyen Tan-Hon and numerous other people since, that when a person listens to "her" protein decided according to the present invention, such as hemoglobin when under anemia condition or rhinovirus inhibitor when catching common cold, the "recognition" of the protein is accompanied by an increase in radial pulse amplitude, followed by a decrease when the "dose" is sufficient; while the result may then be observed as an increase in hemoglobin level or cessation of nose running (See Annex 6, joined testimonies as examples; clinical trials have now begun in Japan in a systematic way). That the "dose" be sufficient may also be controlled by the subjective appreciation of the patient itself. Actually, it was the precise correspondence of this evaluation with radial pulse amplitude variation which led Dr. N'guyen Tan-Hon to his observation. Accordingly, the subjective evaluation of the protein elongation rhythm which one is able to perform using inventor's method may be checked and compared to the speed of the elongation process as directly measured. Table I gives those values for a few common proteins, and Fig. 3 shows the resulting graphs where the phase is clearly visible for every different protein.

11. Viruses or proteins are today commonly considered as strangers within ourselves sometimes very much feared of. Being able to "recognize" and cure a rhinovirus infection, for instance, when listening to its inhibitory sound sequence, now changes this situation. In fact, artistic and in particular musical inspiration has always been a mean, although very limited, of accessing those levels of living being, as evidenced by numerous examples in Dr. Fukagawa's book (and on the Internet). The novelty today is that with the sequencing of the human genome, this may now become a wide access, with the result that the "proteodies" obtained in this way are real medicines, with their powers and dangers. The "Pocket Monster" incident in 1997 in Japan – in which 700 children were sent to the hospital due to a 12-amino acid "inspiration" towards an epileptogenic GABA receptor, as explained in this book – gives an idea of what may happen with a misuse of present invention, which is the main reason why inventor has asked for a patent.

12. Note that the recognition that there are instances, such as in the determination of protein elongation dynamics shown above, where subjective measurement is able to give more

precise results that any objective method, is by itself an important result. This is especially true in view of the fact that as can be understood from a close look at the MEDLINE data bank for any given disease, objective diagnosis provides only a probability for involvement of a given gene's regulation, and the subject is the better placed to recognize whether and to which extent this be the case for him (especially when this may be confirmed using radial pulse control as explained above).

13. The Examiner also contends that experiments done are not "controlled". Not only the experiments such as reported in Dr. Fukagawa's book where always compared with controls, but a recent thesis in Gand University has reproduced several of them with all parameters measured, such as moisture and temperature in different parts of the greenhouse, etc. (See, "Influence of variable sound frequencies on growth and development of plants," Y. van Doorne, (Annexes 7a and 7b). Van Doorne has in particular been able to check the function of tomato extensins, by measuring an average differential increase in plant size of 0.5 cm per day in plants exposed 6 minutes per day to extensin proteolyses, as compared with controls (see figure page 129 and the 50-page statistical analysis at the end of the thesis, performed thanks to the helping supervision of Prof. J. Cumps): in particular no increase in plant nodes was observed, as expected for a pure lengthening of plant cells without increase in their number. In addition, funding has recently been voted to a researcher at INSERM in Paris to perform controlled experiments on cell cultures, using inventor's patented technique. (See Annexes 8a and 8b).

14. Annex 6 shows an increase of the rate of production of haemoglobin (two patients).

15. A further example of the utility of the instant invention is provided by the contract which has been signed on November 2, 2000 with NAGATA Agricultural Research Institute in Japan (Annex 9), and has for object to study the possibility of applying the Inventor's method to enhance the taste of tomatoes, as measured by the sugar content in the fruit, and to improve tomato plant resistance to drought.

16. For the question of indefiniteness of specific claim language, the following may be pointed out:

- As regards the expression "associating with each amino acid a musical note whose frequency is transposed from the proper frequency of the amino acid"; this expression is not

incomprehensible because the proper frequencies of amino acid are described:

- How the musical notes are "decoded and transposed: see Specification, page 8, line 12-page 9, line 21. The calculation was given in an earlier response (calculation array); it relies on the harmonic synchronization phenomenon predicted to occur within the cells between the amino acids frequencies when these lock on their respective tRNA within the time lapse of $10^{-12.5}$ s, similarly to many well-known frequency locking phenomena.

- How the Man skilled in the Art can know that the decoding is correct: when it works and/or when it has been selected by a statistically significant number of patients presumably needing it (an unnecessary or incorrect decoding is normally rejected by the patient). Annex B shows the proteins which have been selected by 10 patients or more of a single therapist, over a four year period (65 proteins out of a set of some 350 routinely used by this therapist). Similar testings are presently officially conducted in St. Marianna University School of Medicine at Kawasaki (Japan), where a new department is being constituted for this purpose.

-the expression "determining the musical periods of said sequence of musical notes by identifying similar series of musical notes" is comprehensible when taken as a whole; for instance, how "spot" musical periods: this is clearly explained in the specification page 10, line 12-page 12, line 21 and examples: page 16, line 12-page 19, line 4 and page 20, line 4-page 21, line 29.

- the expression "tone quality" is not vague and indefinite because the instant Application describes a tone quality at page 14, lines 12-14.

To respond to items (h), (i) and (j) of the Office Action, please note that the adjustment of phrasing to measure is what one does every time one must sing a text while following a rhythmic measure, for instance "Twinkle, twinkle little star how I wonder where you are", where the words "star" and "are" are longer to follow a regular rhythmic, so that the notes and melodic contours ("similar sequences of notes and signatures") match from one measure to the next, as explained

The expression "chromatic tempered scale" (Claims 4 and 5) is not vague and indefinite. This expression corresponds to the definition given at the beginning of the description. English

speaking people use preferably the expression "tempered scale," "equal-tempered scale," or "chromatic scale," instead of "chromatic tempered scale," but the meaning is the same. Reference is given at page 1, lines 4-5; the words "chromatic tempered scale" are used in the English summary of the cited paper; it designates the division of the octave in twelve equal intervals.

- The expression "which are deduced ... with respect to central G" (claim 5) is not vague, indefinite, and incomprehensible because it means that any interval relative to the central G is replaced by the interval of opposite sign; for instance +2 semi-tones (for Q,K,E,M, relative to L,I,N,D) becomes 2 semi-tones, and so on.

- The expression "quantum vibrations associated to the mature protein after it is spatially folded back over itself" (claim 7) is not vague, indefinite, and incomplete because the instant application does describe the properties of such vibration such that one of skill in the art can recognize or detect them. The quantum vibrations are the same as described earlier in the specification., page 9, line 22 - to page 10, line 11; however, they are transposed in a different way (being sealing waves of spatial type, as in reference quoted page 2, line 22 of the specification) according to the formula given to give color frequencies. The information itself is no more temporal (in successive frequency intervals) but positional, i.e., the respective position of colors corresponding to the amino acids positions in the usual 3-D representation of proteins, where every amino acid is represented by a little sphere, colored according to the code given in said claim.

17. To one skilled in the art the term phase in the context of my invention refers to the phase of scaling waves, as quoted on page 2, lines 1 and 2 of the specification. Since the scale resonance effect is due to a match in the sequence of frequency intervals from one amino acid to the next, phase refers to the musical periods as specified page 10 of the specification. Phase opposition in particular refers to the sequence of opposite frequency intervals; thus giving rise to the second code in claim 15, as deduced from the first one (see claim 14).

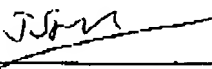
TAS14. Both control tomatoes and the treated tomatoes having 1 ½ litres of water per plant per day. The experiment was replicated in a greenhouse in Grand University by M. Yannick van Doorne, for his thesis in agriculture and bioengineering. He carefully measured all possibly relevant parameters, such as temperature and moisture for both treated and untreated tomatoes and was able to preclude with over 99% probability any of these alternative parameters as the cause of the difference observed; therefore, he was able to conclude that the observed effect was indeed due to the sound treatment. These conditions constitute, therefore, clearly a controlled study.

9. The examiner contends there is no phase in polypeptide elongation, but since various growing nascent polypeptide chains may be seen at a given time in various states of elongation, they are "presumably" also in different phases of elongation. A lot of available evidence contradicts this assumption. First, a periodicity is clearly visible on polyribosomes), and where there is a period, there is a phase. (See Annex 3, figure 1 from B. Alberts et al., Molecular Biology of the Cell, Garland Publishing, New York and London, 3rd edition 1994, p. 238. See annex 4. Second, the existence of a phase in protein synthesis may be checked by comparison with the pauses in elongation as determined from accumulation of intermediate nascent chains of discrete sizes, which may be observed using gel electrophoresis. (See, such as in the work of S. Varenne et al. (J. Mol. Biol. 180, 549-576, 1984), Annex 5. In the example given in this paper on pFW 565 (E. Coli's outer membrane protein A), pauses may not only be seen to fit the musical "cadences" located as explained in patent application (note the average period of amino acids near the maximum amplitude, *i.e.*, maximum number of intermediate nascent chains). The mere fact that they follow a regular pattern, as seen on figure 2 in contradistinction with the predictions of codon usage (which postulate that codon-anticodon binding follows a trial-and-error procedure, wherefrom pauses would simply be statistically correlated with rare codons, yielding a chaotic-like behavior), is by itself evidence of a phase, already in the case of bacteria, with "some" undetermined mechanism to control it – for which inventor's theoretically grounded scaling waves do provide an explanation (the theoretical papers are quoted in application, p. 1 and p.2).

10. In evolved organisms, amino acids are carried through the blood, and are thus subject

In re: Joel Sternheimer
Appl. No.: 09/320,637
Filed: May 26, 1999
Page 8 of 8

18. The undersigned petitioner declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.


Joel Sternheimer
Joel Sternheimer

Date: October 26, 2001